354. EFFECT OF BICYCLOL ON LIVER INJURY INDUCED BY ALCOHOL IN MICE

Chenglin Mo, Ye Li, Yan Li*
Department of New Drug Development, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peiking Union Medical College, Beijing, 100050, P.R. China

Alcoholic liver disease (ALD) encompasses a wide spectrum of lesions, including alcoholic steatosis (fatty liver), alcoholic hepatitis, alcoholic fibrosis and cirrhosis. Bicyclol, a synthetic new drug for the treatment of chronic HBV and HCV, had significant protective effect on the elevation of serum ALT and liver TG; the induction of NDMA-demethylase and the depletion of liver GSH; the pathological alterations such as hepatocyte swelling and fatty degeneration in mice fed with Lieber-Decarli liquid diet containing 5% alcohol for 4 weeks. In addition, the cytosolic ALDH, GST and GR activities were increased by 190%, 40% and 45% after bicyclol pretreatment. Alcohol induced a drastic elevation of alcohol dehydrogenase (150%) and aldehyde dehydrogenase (33%) activity in hepatic mitochondria in mice. After treatment of bicyclol, 46% inhibition of alcohol dehydrogenase and 20% induction of aldehyde dehydrogenase in mitochondria were found in mice subjected to acute alcohol toxicity. The mitochondria membrane fluidity and swelling which reflect the damage of hepatic mitochondria induced by alcohol was also improved by bicyclol treatment. The results suggested that the hepatoprotective effect of bicyclol on liver injury induced by alcohol was partly due to the anti-lipid peroxidation, modulation of alcohol metabolizing enzymes and liver GSH regeneration.

355. ESSENTIAL ROLE OF NRF2 IN PROTECTION AGAINST OVARIAN FOLLICLE LOSS INDUCED BY 4-VINYCYCLOHEXENE AND 4-VINYL-CYCLOHEXENE DIEPOXIDE IN MICE

Xiaoming Hu[1], Jenny Roberts[2], Yuet Wai Kan[3], and Qiang Ma[1]
[1]Receptor Biology Laboratory, Toxicology and Molecular Biology Branch, [2]Pathology and Physiology Research Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV 26505, USA; [3]Laboratory Medicine, Howard Hughes Medical Institute, University of California, San Francisco, CA 94143

Occupational chemicals 4-Vinylcyclohexene (VCH) and 4-vinylcyclohexene diepoxide (VCD) selectively destroy oocytes in small pre-antral follicles leading to premature ovarian failure in animals. Metabolism of VCH and VCD by phase I and phase II enzymes plays important roles in the ovotoxicity. Nrf2 is a member of the CNC bZip family of transcription factors that mediates the basal expression and induction of phase II genes such as *Nqo1* and *Gst*. We examined the role of Nrf2-regulated gene expression in the ovotoxicity of VCH and VCD by using Nrf2 knockout mice. Immature (28 days old) female wild-type and Nrf2 −/− mice were treated with VCH or VCD using established protocols; 4 h following the final dose, ovaries were collected. Complete serial sections of ovaries were evaluated histologically for the presence of follicles. Primordial and primary follicle numbers in ovaries from wild type mice decreased significantly ($p < 0.05$) by either VCH or VCD. However, the follicles in ovaries from Nrf2 −/− mice exhibit much higher sensitive to the toxicity of VCH and VCD than those of wild type. Together, these results demonstrate that loss of Nrf2 function is associated with increased sensitivity to toxicity of VCH and VCD on ovary follicular development. Currently, phase II enzyme-related mechanisms are being investigated in ovaries for increased sensitivity to ovarian toxicity of VCH and VCD.

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